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PULSE

A Monthly Update on Advances in Neuromodulation
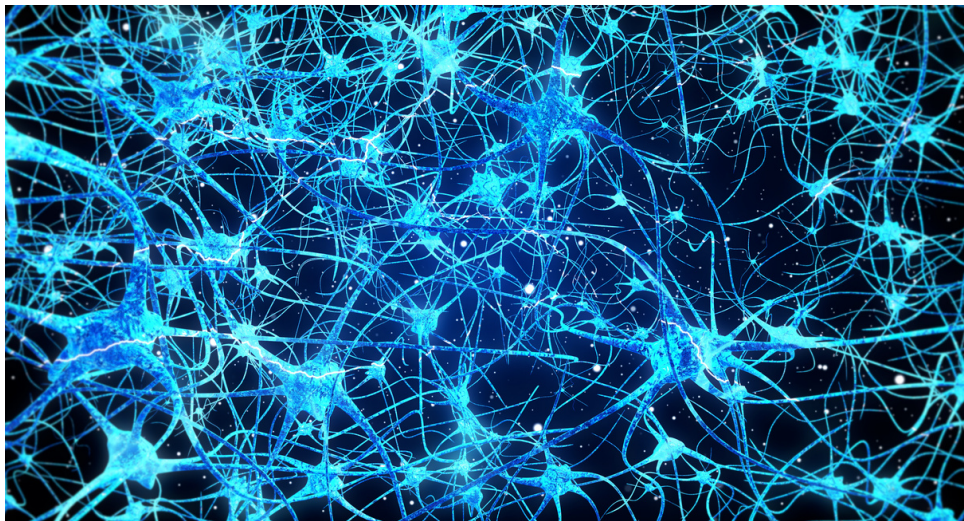
Different Symptom Rating Scales Confer Varying Abilities to Detect rTMS Treatment Response in TRD

Erin M Hegarty, MD reviewing Leuchter et al., Psychiatry Research 2023 December

This large, naturalistic study of patients undergoing routine clinical rTMS for treatment-resistant depression compared the performance of four different depression rating scales (three self-rated and one observer-rated) for detecting clinical response and remission. The authors found that all scales demonstrated the ability to identify signs of early response and non-remission. The PHQ-9, one of the most common self-report scales, was the most likely to detect beneficial changes and the least likely to overlook response/remission.

Most psychiatric mood rating scales were designed to measure outcomes associated with pharmacologic therapy and/or behavioral psychotherapy. However, rTMS has a very different mechanism of

action, and rating scale performance in rTMS has not been well-assessed. Certain scales may underestimate (or miss entirely) the response to rTMS. Furthermore, there is wide variability in patient response rates to rTMS, with rates ranging from 30% to 60%. The authors of this study sought to examine this apparent variability in scale performance in a clinical setting, aiming to assess which scales may be preferable for accurately capturing rTMS-related antidepressant effects.

This naturalistic study examined symptom rating scores in 708 patients with treatment-resistant non-psychotic depression at UCLA receiving a complete routine clinical course of 30 sessions of rTMS over six weeks. Symptoms were assessed weekly using four different rating scales: the Patient Health Questionnaire (PHQ-9), Inventory of Depressive Symptomatology (IDS), Profile of Mood States (POMS), and Hamilton Depression Rating Scale (HDRS). Standard definitions of response and remission were utilized, though an empiric definition of remission on the POMS was generated. Protocol parameters were adjusted using a measurement-based care paradigm that included augmentation stimulation sites in those not demonstrating response. Each scale was examined both as a continuous and categorical outcome (i.e., nonresponse, response, or remission on a scale). Agreement between scales was assessed through a series of Kendall rank correlations throughout treatment. Next, linear mixed models were generated looking at scale score by outcome group to examine differences in trajectories between responders, remitters, and nonresponders. Lastly, Cox Proportional Hazard models were generated to study differences in

the predictive value of each scale to predict the time to response or time to remission by scale. This allowed for the assessment of positive and negative predictive values (PPV and NPV) of common clinically utilized markers of early treatment response (percent improvement after 1 and 2 weeks of treatment).

All scales were able to detect response to treatment, but the rates of both response and remission differed between them, with the PHQ-9 most likely to detect response (50% response, 14% missed response seen by another scale) to treatment and least likely to miss it. The IDS, POMS, and PHQ9 performed equally in detecting remission. Fifty-four percent of patients were considered responders, and 32% were remitters by at least one scale. Rank correlation between self- and observer-report scales increased over time, suggesting that patient insight regarding their degree of improvement increased with more treatment. Mixed models showed significant differences in the trajectory of improvement by outcome group on all scales. Proportional Hazards models showed higher baseline scores (more severe symptoms before treatment) were predictive of non-remission in all four scales. However, higher scores on the PHQ9 and HDRS were not predictive of non-response. Generating predictive values for early improvement of ≥10% after session 5 (PPVs 57-76% response, 18-43% remission; NPVs 56-72% response, 76-84% remission) or ≥20% after session 10 (PPVs 65-82% response, 25-50% remission; NPVs 63-77% response, 83-87% remission), the authors found scales were generally better at identifying early signs of response than nonresponse and non-remission than remission (though with some variability, particularly in the IDS).

Impact: This study found variable performance in rating scales over the course of rTMS treatment, with differing abilities to identify responders, remitters, and non-responders across the four scales studied. The PHQ-9 was most likely to detect a meaningful response, and the HDRS yielded the lowest response and remission rates, which is in notable contrast to previous studies finding observer reports more likely to detect response to medication and therapy. While the sources of variability between scales and deviation from prior work are unclear, it is clear that using a single rating scale confers a substantial risk of missing response or non-response to treatment. Clinically, we often use a single rating scale, but with this risk of misclassifying treatment outcomes (at least in rTMS), the authors recommend the use of multiple rating scales for a more thorough characterization of symptom changes. Of course, the choice of scales in any individual setting will vary and can even be tailored to an individual patient's predominant symptoms. Future work further characterizing symptom changes over time or using these findings to inform the development of a fit-for-purpose scale would be of great interest to the field.

Leuchter MK, Citrenbaum C, Wilson AC, et al. A comparison of self- and observer-rated scales for detecting clinical improvement during repetitive transcranial stimulation (rTMS) treatment of depression. Psychiatry Res. 2023;330:115608.

Pain Relief for Temporomandibular Disorders (TMD) After Single rTMS Session

Lara Tang reviewing Babiloni et al., J Oral Rehabil Jan 2024
This randomized, double-blind trial suggests that a single session of rTMS over the motor cortex may have mild immediate analgesic effects for women with painful TMD.

Painful temporomandibular disorder (TMD) is a common, chronic disorder that affects over one-third of adults aged 20–49. Though rTMS is typically studied as a therapy for psychiatric disorders, there is much (and further increasing) evidence to support its use in the realm of chronic pain conditions. However, few studies have investigated rTMS' applications to chronic temporomandibular pain. Might rTMS, perhaps even one session, meaningfully decrease the pain levels of patients with temporomandibular disorders?

This randomized controlled crossover trial of 41 female participants (ages 18 to 65, mean age 26.63) with painful TMD compared active and sham rTMS delivered to the motor cortex (M1). Active stimulation consisted of 1500 pulses of 20 Hz stimulation at 80% MT in 50-pulse trains with a 30-second ITI. During the first study visit, the MT was checked and the M1 region determined for each participant, and they were asked to complete twice-daily pain diary entries monitoring pain intensity and unpleasantness (using standardized visual analogue scale [VAS] ratings of pain and sleep alongside diary adaptations of the pain catastrophizing scale and positive and negative affect scale) for the duration of the study (21 days). At the second visit, patients received either active or sham stimulation and were asked about their pain levels (using a standardized VAS for pain and the Gracely Box Scale [GBS] for unpleasantness) immediately before and after the intervention. At the third visit, patients received the other form of stimulation. All visits were spaced seven days apart. Analyses examined immediate pre- and post-rTMS session changes and longitudinal changes using Mixed ANOVAs and nested multilevel regression models.

Subjects experienced a significant immediate decrease in pain intensity from before relative to after rTMS treatment only in the active group (VAS reduction from 29.42 to 21.48, p<.001) and immediate decreases in intrusiveness in both groups (active GBS =7.31 to 5.37, p < .001; sham GBS= 6.56 to 5.98, p = .011). However, longitudinal examination over the week following intervention revealed reductions in both pain intensity and unpleasantness in both groups, with no difference between groups. Similarly, there were significant differences in self-reported pain interference and sleep quality before and after both interventions, but not between the sham and rTMS groups.

Impact: This study demonstrated that a single session of rTMS may have mild, immediate analgesic effects for those experiencing painful TMD. This finding is significant for the clinical treatment of those suffering from chronic temporomandibular pain, offering rTMS as a non-invasive therapy for TMD. It also contributes to understanding how rTMS may alter the cortical pathways involved in pain regulation. Though this study did not focus on longitudinal effects, the preliminary improvements with single sessions are encouraging, even if matched by sham in this study. Further research discerning the duration and frequency of treatment to achieve longer-term analgesic effects for those with painful TMD would be of great interest in the field of chronic pain.

Babiloni AH, Provost C, Charlebois-Plante C, et al. One session of repetitive transcranial magnetic stimulation induces mild and transient analgesic effects among female individuals with painful temporomandibular disorders. J Oral Rehabil. Published online January 15, 2024. doi:10.1111/joor.13655

Two Potential "Sweet Spots" for Deep Brain Stimulation (DBS) In Obsessive Compulsive Disorder (OCD) Identified

Miguel Serrano-Illan, MD, PhD, reviewing Meyer G et al. Biol Psych 2023 Dec 21

This retrospective study of patients who underwent DBS implantation for OCD in the ventral capsule/ventral striatal region identified the greatest response of OCD symptoms in those whose electrodes were nearest to two specific locations within that region, specifically the anterior limb of the internal capsule and the inferior thalamic peduncle/bed nucleus of the stria terminalis.

Intrusive thoughts and repetitive behaviors characterize obsessive-compulsive disorder (OCD), and approximately half of patients fail to respond to routine medication and psychotherapeutic treatments. Deep brain stimulation (DBS) involves the surgical implantation of electrodes to stimulate specific parts of the brain; it is utilized in the most treatment-resistant cases of OCD, primarily through

targeting the ventral capsule and striatum (VC/VS) region. While a range of targets for DBS for OCD have been proposed, optimal sites within the VC/VS region are still unclear. In this retrospective study, the authors analyzed a multi-center cohort of OCD patients to study the areas within the VC/VS region associated with the greatest improvement.

A cohort of 80 treatment-resistant OCD patients (27 female, 31 male, mean age at surgery 41.1 ± 12.5 years) from eight different DBS centers (partitioned into 58 as a discovery set for model building and 22 as a validation set for the model) who underwent bilateral DBS implantation of the VC/VS region were assessed. Electrode localization was performed using the Lead-DBS toolbox and E-field calculations from imaging data. This allowed for the utilization of a technique called sweet-spot mapping, which involves calculating the correlation coefficients between the strength of the electric field from DBS and symptom improvement in a voxel-wise

manner across the entire cohort of patients at once. Ultrahigh-resolution MRI templates were used to overlay the contact locations of electrodes in the brain and then cross-validated by correlating them to YBOCS improvements. Clinical assessment using the YBOCS score for OCD and other validated depression and anxiety measures was conducted post-operatively, with the YBOCS score being the focus of this study.

In the discovery/experimental group, YBOCS scores improved by 38.3+/- 23.8%, and nearly half of the patients responded (defined as Y-BOCS improvement of ≥35%) to DBS, with more modest improvements in depression (23.0 +/- 53.0%) and anxiety (17.2+/- 31.6%). Unsurprisingly, improvements in OCD correlated with depression (4=0.49, p=0.001) and anxiety (r=0.47, p=0.006). Using sweet spot mapping, two optimal sites (in both hemispheres) for DBS were identified: one in the anterior limb of the internal capsule and another near the inferior thalamic peduncle and bed nucleus of the stria terminalis. Increases in sweet spot scores near these

regions correlated with YBOCS improvement (r=0.36, p=0.003). Of note, the nucleus accumbens and anterior commissure were also linked to positive, though less optimal, results. The anterior site was also associated with better outcomes for depression and anxiety, while the posterior site mainly improved depression. These sites are also consistent with and anatomically close to previously reported optimal sites for DBS.

Impact: This study accomplishes two goals: firstly, it provides further evidence that appropriately targeted DBS can improve OCD treatment outcomes. Secondly, it provides guidance for refining DBS electrode placement to be validated by future work. This will hopefully enhance the efficacy of OCD and comorbid conditions with DBS therapy and aid in the development of standardized approaches for DBS for psychiatric conditions.

Meyer, G. M., Hollunder, B., Li, N., Butenko, K., Dembek, T. A., Hart, L., Nombela, C., Mosley, P., Akram, H., Acevedo, N., Borron, B. M., Chou, T., Castaño Montoya, J. P., Strange, B., Barcia, J. A., Tyagi, H., Castle, D. J., Smith, A. H., Choi, K. S., Kopell, B. H., … Horn, A. (2023). Deep Brain Stimulation for Obsessive-Compulsive Disorder: Optimal stimulation sites. Biological psychiatry, S0006-3223(23)01785-7. Advance online publication. https://doi.org/10.1016/j.biopsych.2023.12.010

Broad-field rTMS Demonstrated to be Effective for Late-Life Depression

Michael K. Leuchter, MD reviewing Roth et al. J Clinical Medicine 2024 Jan 31

This open-label phase IV study of the Brainsway H1 coil demonstrates that rTMS using this broader coil appears effective for depression in older adults in addition to prior studies showing its effectiveness in younger adults.

MDD in adults over the age of 60, referred to as late-life depression (LLD), is becoming increasingly prevalent, and between 55 and 81% of those with LLD do not respond to first-line antidepressants. In the setting of medication non-response, side effect burden, and polypharmacy, treatment options with fewer risks and greater benefits are necessary. While rTMS has been examined as

a treatment option for older adults, initial evidence suggested it was less effective in older adults than younger ones. Over time, this initial evidence has been challenged. As evidence supports the use of rTMS with a traditional figure of 8 coils for LLD, what about deep/broad rTMS using an H1 coil, which stimulates bilaterally?

This open-label phase IV study

examines clinical outcomes in LLD in a group of 247 participants (ages 60-91, mean 70.2±6.1; 62% female; 96% white; current episode duration 21.5±21.5 months; history of 8.5±5.1 episodes and 12±5 medication trials) from 2018-2021 spread over 16 sites. Treatment consisted of once-daily sessions of 1980 pulses in 55 trains of 18Hz stimulation with a 20-second

ITI delivered to the DLPFC. The Participants examined included those who had received at least 20 (n=247) and at least 30 (n=68) sessions. Clinical assessments included a mix of the BDI-II, PHQ-9, and HDRS, with different sites using different scales to varying degrees and frequencies. The authors provide descriptive outcomes of response and remission rates and time to response in their analyses.

After 20 treatments, 69.2% of participants demonstrated a response on at least one scale (whichever a participant had most frequently completed was utilized in this analysis), with 42.1% achieving remission. After 30 treatments, these rates increased to 79.4% response and 60.3% remission. Within individual scales, the HDRS demonstrated the greatest response and remission rates, though they had quite small sample sizes (n=15 at session 20, n=9 at session 30), followed by the PHQ-9 and then BDI-II. The median time to response was determined to be 14 sessions, and the median time to remission was 15 sessions. There were no reported significant adverse events, though there were notably fewer participants with data available at session 30 than at session 20 for unclear reasons.

Impact: This study further supports using rTMS as a treatment for LLD. It additionally shows high response and remission rates compared to many other studies, indicating that prior work suggesting bilateral stimulation confers additional benefit beyond unilateral in rTMS for LLD may warrant further exploration. Clinicians considering treatment options in LLD should keep in mind these impressive outcomes and utilize rTMS earlier in treatment to reduce polypharmacy and other risks associated with medications.

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cTBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
ECT (electroconvulsive therapy)
HFL (high frequency left, 10 Hz stimulation to left DLPFC)
HF-rTMS (high frequency repetitive transcranial magnetic stimulation; 10 Hz unless otherwise stated)
iTBS (intermittent theta burst stimulation)
MST (magnetic seizure therapy)
TBS (theta-burst stimulation; TMS delivered as triplet burst pulses at 50 Hz, repeated at 5 Hz)
TENS (transcutaneous electrical nerve stimulation)
TMS (transcranial magnetic stimulation)
rTMS (repetitive transcranial magnetic stimulation)
tDCS (transcranial direct current stimulation)
tACS (transcranial alternating current stimulation)

BOLD (blood oxygen level dependent)
DTI (diffusion tensor imaging)
EEG (electroencephalography)
EMG (electromyography)
fMRI (functional magnetic resonance imaging)
MRI (magnetic resonance imaging)
MT (motor threshold)
RMT (resting MT)

ADHD (attention-deficit/hyperactivity disorder)
AUD (alcohol use disorder)
GAD (generalized anxiety disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive disorder)
PTSD (post-traumatic stress disorder)
SUD (substance use disorder)
TRD (treatment resistant depression)

BAI (Beck Anxiety Inventory)
BDI (Beck Depression Inventory)
CGI (clinical global impression scale)
HAM-A (Hamilton Anxiety Rating Scale)
HAM-D / HDRS (Hamilton Depression Rating Scale)
MADRS (Montgomery-Asberg Depression Rating Scale)
MoCA (Montreal Cognitive Assessment)
PANSS (Positive and Negative Symptom Scale)
QIDS (Quick Inventory of Depressive Symptomatology)
YBOCS (Yale-Brown Obsessive Compulsive Scale)

ANOVA (analysis of variance)
AUC (area under the curve)
CI (confidence interval)
FDA (United States Food and Drug Administration)
ICA (independent component analysis)
ITT (intention to treat)
OR (odds ratio)
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
RCT (randomized controlled trial)
ROC (receiver operating characteristic)
SMD (standard mean difference)

BA (Brodmann area)
DLPFC (dorsolateral prefrontal cortex)
DMPFC (dorsomedial prefrontal cortex)
M1 (primary motor cortex)
mPFC (medial prefrontal cortex)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)

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